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August 7, 2002

Paul E. Helliker
Director
Department of Pesticide Regulation
1001 I Street
P.O. Box 4015
Sacramento, California 95812

Dear Mr. Helliker:

With this letter I am pleased to transmit to you the Scientific Review Panel on Toxic Air Contaminants' Findings on Metam Sodium and other Pesticidal Sources of Methyl Isothiocyanate. The findings were based on the Panel's review of the Department of Pesticide Regulation's draft report titled "Evaluation of Methyl Isothiocyanate (MITC) as a Toxic Air Contaminant."

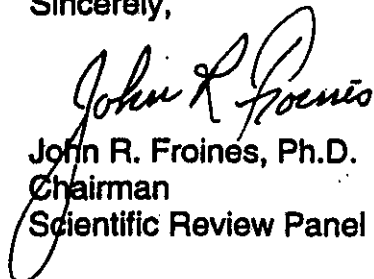
The Panel reviewed the draft report as well as the scientific data on which the report is based, the scientific procedures and methods used to support the data, and the conclusions and assessments on which the report is based, as required by state law. The Panel also reviewed comments received and responses to those comments. In approving the report, it is the Panel's conclusion that the report, with the revisions requested by the Panel, is based on sound scientific knowledge.

The Panel recommends that you take the necessary regulatory steps to list methyl isothiocyanate as a toxic air contaminant. The Panel notes that methyl isothiocyanate is in the ambient air largely as a result of the breakdown of metam sodium, with smaller contributions from other pesticides such as metam potassium and dazomet. Therefore, the Panel also recommends that the Department of Pesticide Regulation take steps to regulate all pesticidal sources of methyl isothiocyanate. Finally, the Panel discussed and found that some breakdown products of metam sodium that are of concern, such as methyl isocyanate, are already considered toxic air contaminants under state law by already being listed as federal hazardous air pollutants. However, other breakdown products such as hydrogen sulfide are not listed, and should be identified as toxic air contaminants.

Let me also take this opportunity to thank the Department of Pesticide Regulation staff for their efforts in completing this report. The Panel appreciates the time and work that were put into the report as well as responding to further questions from the Panel.

Lastly, we ask that the Panel's findings and this letter be made a part of the final report.

Sincerely,



John R. Froines, Ph.D.
Chairman
Scientific Review Panel

cc: Scientific Review Panel members

Joan E. Denton, Ph.D., Director
Office of Environmental Health Hazard Assessment

Alan C. Lloyd, Ph.D., Chairman
Air Resources Board

Jim Behrmann
Liaison, Scientific Review Panel

Enclosure

**Scientific Review Panel findings
on metam sodium and other pesticidal sources of methyl isothiocyanate
(The Department of Pesticide Regulation's document is entitled "Evaluation of methyl
isothiocyanate (MITC) as a toxic air contaminant").**

Use and Environmental Fate

1. Pesticidal use of MITC is infrequent in California, but MITC is the primary breakdown product and active principle of the highly used pesticide, metam-sodium. Agricultural use of metam-potassium and dazomet also produces MITC.
2. Nearly fifteen million pounds of metam-sodium were used in California in 1998, mainly for agricultural fumigation. The highest use occurs in Kern, Imperial and Fresno Counties. California use of metam-sodium more than doubled between 1990 and 1998.
3. Metam-sodium in soil is converted to MITC within the first 24 hours after application, depending on soil temperature and moisture. MITC diffuses through soil; a major portion is eventually lost by volatilization to air. Thus, while metam sodium is itself non-volatile, its application results in significant production and emission of air contaminants.
4. The half-life of MITC in air was reported as 29 to 39 hours in natural sunlight. MITC in air degrades by photolytic decomposition, in part to methyl isocyanate (MIC). MIC may be photochemically stable. Methyl isocyanide and N-methylformamide were identified as other possible breakdown products of MITC.
5. Metam-sodium decomposition can result in the formation of several other toxic chemicals including carbon disulfide (CS₂), methylamine, and hydrogen sulfide (H₂S). In practice, degradation to H₂S and MITC (and then to MIC) is favored.
6. Dazomet and metam potassium are two other pesticides registered for use as soil fumigants that produce MITC as the active agent. However, only 16,000 pounds of Dazomet and 9,200 pounds of metam-potassium were reported in 1998; metam sodium is the dominant agricultural source of MITC and MIC in California air.

Exposure associated with metam-sodium application

7. DPR's evaluation document summarizes six studies that measured airborne MITC at fields treated with of metam-sodium (application site studies). In two of these, the soil was sealed after application consistent with current label requirements. MITC measurements from the other four application site studies are presented as supporting data. The maximal air concentrations of MITC reported in the application studies may represent an upper-bound on exposure concentrations likely to be encountered immediately adjacent to metam-sodium treated fields in California. Three studies of MITC in ambient air in and near homes were described. While sampling in the ambient studies did not necessarily coincide with applications of metam-sodium in the area, the studies were carried out in high use areas of California. In one of the ambient studies, samples were mis-handled to the extent that the

data are not useful for exposure characterization.

8. DPR adjusted the measured air concentrations in all the exposure studies for field recovery percents (67-100%). Further, if the rate of metam sodium application was less than the maximum allowed, the resulting MITC concentrations were scaled linearly to the concentration that would be expected if the application had been at the maximal label-approved rate.
9. DPR computed short-term (1, 8, and 24 hour) air concentrations of MITC from measurements reported in the six application-site studies. Samplers were located from 5-970 meters from field edges. The highest one hour concentrations from each study ranged from 281-2853 ppb; the highest 24 hour concentrations (averaged from samples of shorter duration) range from 175-1102 ppb. Maximal measurements were taken just 5 meters from the field perimeter; inside current buffer zones.
10. Moderate-term (>2 day) air concentrations were computed for all application site studies by developing time-weighted averages for the measurements at each location over the length of the sampling period. The resulting values were used in margin-of-exposure (MOE) analysis of seasonal exposures.
11. MITC concentrations measured in ambient exposure studies were considerably lower than the concentrations adjacent to field applications. The two viable ambient studies produced moderate term air concentrations between 0.13-4.09 ppb, considerably lower than estimates of maximal seasonal exposures for people immediately adjacent to application sites. The Panel notes the limitations of the ambient air studies to represent actual population exposures in California's agricultural areas. Exposure is expected to vary considerably both temporally and spatially. The available data for MITC are insufficient for an adequate characterization of the distributions that underlie the observed variability in exposures.
12. Air concentrations of metam sodium breakdown products other than MITC were not determined in most exposure studies. However, a study by the Air Resources Board in Kern County in 1995 found application site concentrations of MIC from 0.09 to 2.5 ppb (12 hr. time-weighted average). Concurrent 12 hour measurements of MITC concentrations ranged from 0.08 to 84 ppb. H₂S concentrations up to 76 ppb were detected in samples collected from 1-4 hours post-application, in a monitoring study conducted by DPR in 1993.
13. Human exposure to atmospheric breakdown products of metam sodium can occur by both inhalation and dermal routes; the predominant exposure route is inhalation. No dermal toxicity endpoints were used in the risk appraisal.

Human Health Effects associated with Metam-Sodium Applications and Spills

14. A large spill of metam-sodium occurred in conjunction with a train derailment near Dunsuir, California in 1991. As a consequence, the volatile breakdown products of metam-sodium were released into local air. The most frequently reported signs and

symptoms among those exposed were nausea, headache, throat irritation, dizziness, vomiting and shortness of breath. Exposure levels are uncertain, but have been estimated by modeling. Three different modeling approaches estimated peak concentrations within 100 meters of the spill at 650, 1300, and 4500 ppb.

15. One report documented cases of persistent irritant-induced asthma and exacerbation of asthma in persons exposed to metam-sodium breakdown products as a result of the Dunsmuir spill. Exposure to respiratory irritants, such as MITC and MIC, can cause prolonged adverse effects including reactive airways dysfunction syndrome (RADS), a form of chemically-induced asthma.
16. Excluding the Dunsmuir incident, 390 case reports associated with metam-sodium applications were received by the California Pesticide Illness Surveillance Program between 1990 and 1999. Ocular signs and symptoms included watery, burning and itchy eyes and blurred vision. Systemic signs and symptoms included nausea, diarrhea, weakness, dizziness, headache, and vomiting. Respiratory signs and symptoms included cough and shortness of breath.
17. An application of metam sodium in Earlimart, California in 1999 caused 173 individuals, including 2 emergency response personnel, to report exposure-related illness. Neighborhood evacuations fear and medical expense also contributed to a considerable impact on the community. Irritation of the eyes, nose and/or throat was noted in the majority of complaints. There were 5 cases of asthma exacerbation and 23 people with dyspnea, chest pain and/or cough. 8 cases of rash were identified. Exposure levels are unknown. Air dispersion modeling by DPR estimated that the majority of those who filed odor complaints or reported illness were likely exposed to a 1-hour time-weighted average (TWA) concentration between 0.5 and 1 ppm. Adjacent to the field, 1 hour TWAs were estimated to be 3 ppm. Modeling, while highly uncertain, also suggests that some illness could have occurred at 1 hr. TWA concentrations below 0.5 ppm, near the experimentally defined NOEL for MITC. Exposure to other breakdown products of metam sodium was not modeled, and it is not known to what extent MITC and/or other products contributed to illness in Earlimart. Whether exposure to the suite of breakdown products can cause illness at MITC levels that would not induce effects in the absence of the other compounds remains an important question for risk management of metam sodium (see findings # 44 and 45, below.)

Exposure of Experimental Animals to Metam-Sodium in Drinking Water

18. Metam-sodium in aqueous solution produces MITC. Therefore, drinking water administration of metam-sodium to laboratory animals may provide data relevant to the toxicological evaluation of MITC in air. The available drinking water studies did not, however, quantify the MITC present in metam-sodium treated water.
19. Subchronic exposure of mice and rats to metam-sodium in drinking water produced decrements in body weight gain, food consumption and water intake. These findings are similar to results noted in MITC treated animals (finding #24).

20. Chronic exposure to metam-sodium via drinking water produced angiosarcomas in male mice and rats; the draft TAC evaluation document did not provide detailed data.

Human Health effects of MITC exposure

21. One controlled exposure experiment with MITC in humans has been conducted to date. Increased blink rate and irritation, as measured on a subjective scale, were observed during exposures to 0.8, 1.9, and/or 3.3 ppm MITC. Whether effects were observed at a particular exposure level depended upon the duration of exposure. No significant effects were observed in groups of subjects exposed to 220 ppb MITC for 4 or 8 hours. In all experiments, exposure was to the eyes only; respiratory irritation could not be evaluated.
22. Two clinical reports suggest that MITC could cause dermal reactions in humans, consistent with limited evidence of skin rash from the Earlimart incident (finding #17).

Exposure of Experimental Animals to MITC

23. Acute toxicity of MITC has been studied in a variety of animal species including rats, mice, rabbits, dogs, cats, guinea pigs and monkeys. Acute effects in rats following inhalation exposure included hyperactivity, hypoactivity, eye irritation and increased respiratory rate. In rabbits, MITC was shown to be a severe skin and eye irritant. MITC may be a dermal sensitizer in guinea pigs, in agreement with limited evidence in humans (finding #22).
24. Adverse effects have been reported in subchronic toxicity studies of MITC in laboratory animals following inhalation, gavage or dietary, and dermal administration. Effects noted in a 4 week inhalation exposure in rats included nasal epithelial atrophy at all exposure levels tested, with increased pathology of the respiratory tract at the highest exposure. Effects observed at the highest concentration of 34 ppm included bronchopneumonia, epithelial proliferation, rhinitis, tracheal necrosis, and squamous metaplasia. In a 90 day inhalation study in rats, effects included decreased body weight gain, decreased food consumption, nasal discharge, decreased serum protein and mortality; histopathological examination was not performed in the 90 study.
25. Chronic oral toxicity studies of MITC have been conducted in dogs, rats and mice; no chronic studies of inhalation exposure were identified. A suggestion of oncogenic potential was noted in rats and mice exposed to MITC in drinking water. In female rats given 2, 10 or 50 ppm of MITC in the drinking water for 104 weeks, the incidence of benign and malignant mammary gland tumors was significantly higher in the 10 ppm, but not in the 2 or 50 ppm groups. A comparison of controls versus all MITC exposed animals did not show a statistically significant increase in overall tumor incidence. In the mouse drinking water study, a small increase in cutaneous fibrosarcomas was observed in the highest dose group of both males and females. When the data from both sexes are combined, the increase in tumor incidence (from 0% to 4.3%), is statistically significant ($p < 0.05$). In conclusion, there is a suggestion of animal carcinogenicity, but the data are inadequate and further investigation is required.

26. MITC has been tested for genotoxicity in microorganisms, cultured mammalian cells and laboratory rodents. Most study results were negative. A technically limited evaluation of chromosomal effects in Chinese hamster V79 cells indicated a weakly positive response.
27. No reproductive effects were identified in a two-generation drinking water study in rats or in a three-generation oral gavage study in rats. Mild systemic effects observed included decreased water consumption and occasional decrements in weight gain compared to untreated animals. In a 3 month oral gavage study in mice and rats, mild decrements in spermatogenesis and decreased ovary weights were noted in both species.
28. Three developmental toxicity studies were reviewed, one in rats and two in rabbits. These studies showed decreased fetal body weight and size at doses that also produced maternal adverse effects such as decreased feed consumption and body weight gain. The maternal effects were noted in both species.

Health Effects of MIC

29. MIC is highly toxic. Accidental release of 30 to 35 tons of MIC from a pesticide factory in Bhopal, India, caused thousands of deaths by acute respiratory failure. Survivors suffered skin and eye injuries, shortness of breath, chest pains, cough, throat irritation, choking and hemoptysis (expectoration of blood). Objective signs of the corrosive effects of MIC on the respiratory tract were interstitial and alveolar edema and destructive lung lesions with cavitation, alveolar wall thickening and interstitial fibrosis. Pulmonary function tests indicated lung volume, air flow and pulmonary vascular impairments. Bronchiolitis obliterans was a long term result of the acute lung injury. MIC exposure concentrations in the Bhopal accident were estimated to be between 13 and 100 ppm. Many of the acute and chronic signs observed in humans have been reproduced in experimental laboratory experiments (mice and rats).
30. In three controlled exposures of human volunteers to MIC, eye irritation and lacrimation were observed after exposures ranging from 0.5 ppm to 5 ppm for 10 seconds to 50 minutes.
31. MIC exposure has severe consequences for fetal and neonatal survival. In Bhopal, fetal loss rose from an estimated normal incidence rate for that area of 6-10%, to 43% in the exposed population. Mortality among infants exposed *in utero* increased over four-fold, from 2.6-3% in the 30 days after birth during the 2 years preceding the accident, to 14% after the disaster. Animal data support this finding: pregnant mice exposed to 1 ppm MIC for 6 hours/day on gestation days 14-17 had a 3.3% fetal mortality rate, compared to 0.4% in controls.
32. MIC has tested positive in several assays for genotoxicity, including tests for chromosomal damage and point mutation, *in vitro* and *in vivo*. In Bhopal survivors, chromosomal aberrations in peripheral lymphocytes were noted 2.5 months after the accident. The findings of clastogenicity and genotoxicity suggest that MIC could have oncogenic potential. However, in the only oncogenicity study identified, mice were exposed for just two hours, which did not result in tumor production. Whether MIC is oncogenic remains unknown.

Health Effects of Other By-Products of Metam Sodium Use

33. Brief summaries of the toxicity of hydrogen sulfide, carbon disulfide, methylamine, and carbonyl sulfide are provided in the TAC evaluation. Based on the limited available exposure information, H₂S poses the greatest exposure concern of these compounds. H₂S is a highly toxic, irritant gas that causes respiratory symptoms and eye irritation after acute exposure. At high concentration it paralyzes the sense of smell. Airborne concentrations of 700 ppm and more cause immediate death through cytotoxic asphyxia.

Human Health Risks

34. Risks of exposure to metam-sodium were not assessed for this document because metam sodium is not present in air after agricultural use.
35. Eye irritation in human volunteers was chosen as the critical endpoint for acute exposure to MITC. DPR identified an acute lowest observed adverse effect level (LOAEL) for eye irritation of 800 ppb and an acute no observed adverse effect level (NOAEL) of 220 ppb.
36. A subchronic LOAEL of 1.7 ppm MITC was identified from a 4 week inhalation study in rats, based on increased atrophy of the nasal epithelium in exposed animals compared to controls. A subchronic NOAEL of 100 ppb was estimated from the LOAEL by adjusting to continuous exposure and applying an uncertainty factor of 3. Benchmark dose analysis of the dose-response data yields similar results.
37. Margins of exposure (MOEs) for acute exposures to MITC near field applications of metam-sodium were computed as the ratio of the NOAEL for eye irritation to observed air concentrations. Because the ratio in this case involves an effect level derived from a human study, a MOE of at least 10 beyond the no-effect level is considered to be protective; MOEs less than 10 indicate risk. Using the maximal exposure levels reported in application site studies, acute MOEs ranged from <1 to 17; all but 2 MOEs were less than 10. The acute exposures as measured thus indicate potential risk of eye irritation to bystanders.
38. MOEs for seasonal exposures at application sites were computed as the ratio of the subchronic NOAEL (finding #36) to moderate-term air concentrations (after adjustment to 23/120 days. Because these ratios compare human exposure to no effect levels in animals, a MOE must be at least 100 to be considered protective. The MOEs for seasonal exposure ranged from 1-50, indicating potential risks to those exposed at metam-sodium treated fields on a repeated basis during the season of use.
39. Reference exposure levels (REL) for acute, seasonal and chronic exposures developed by DPR are in Table 1. . Because toxicological data on chronic inhalation exposure to MITC are lacking, DPR's chronic REL was based on the NOAEL for nasal epithelial atrophy estimated from the 28 day inhalation study in rats.

Table 1. NOAELs and RELs for acute, seasonal and chronic exposures to MITC

Species	NOAEL	REL
<i>Acute</i> Human	220 ppb	22 ppb
<i>Seasonal (subchronic)</i> Rat Human	100 ppb (estimated from LOAEL)	1 ppb
<i>Chronic</i> Rat (subchronic study) Human	100 ppb (estimated from LOAEL)	0.1 ppb

40. DPR developed a NOAEL and REL for acute exposure to MIC. A LOAEL of 500 ppb for a 10 minute exposure was selected from the three available studies of human eye irritation (finding #30). This yielded an acute REL of 0.98 ppb.
41. The highest MIC concentration measured after application of metam-sodium in the one available data set was 2.5 ppb (12 hour sample), exceeding the one hour REL of 0.98 ppb. The concentration of MITC during the same period was 67 ppb. Since all six studies of metam-sodium application reported maximum 24-hour MITC levels higher than 67 ppb (finding #9), MIC may have been present in concentrations greater than 2.5 ppb as well. While DPR did not carry out an MOE analysis for MIC due to very limited data, these results suggest a potential risk associated with acute exposures. It is important that greater effort be directed to determining levels of MIC present in air after application of metam sodium so that overexposure to this highly toxic compound can be avoided.
42. Concentrations of hydrogen sulfide related to metam-sodium applications were measured in only one of the available studies. The report noted that the highest measured concentration, 76 ppb, is more than twice the California Ambient Air Quality Standard of 30 ppb. There is a need for better data and control of exposure at metam-sodium treated fields, similar to that noted for MIC.

Uncertainties and Other Relevant Findings

43. Little is known about the variability in human inhalation exposures to pesticides and their breakdown products. How representative the exposure studies reported here are for other locations with metam-sodium use is not known. Distributions of ambient exposures are particularly complex and difficult to characterize with currently available data.
44. Following agricultural metam-sodium applications, inhalation exposure is not limited to MITC, but may also include other degradation products such as CS₂, H₂S and MIC. There is uncertainty about how these breakdown products interact to produce the overall potential toxicity deriving from the use of metam-sodium, but MITC, MIC and H₂S have all been

associated with ocular and respiratory irritation. DPR concluded that, while there are no data to address mixed exposure, additive or synergistic effects of MITC, MIC and H₂S in respiratory and ocular tissues are plausible. If both the modeled exposure estimates for MITC in Earlimart (finding #17) and the experimentally derived NOEL for MITC (220 ppb) are accurate, then some illnesses in Earlimart may have been produced at MITC concentrations near the NOEL because of exposure to the mixture of breakdown products.

45. The limited data available indicate that MIC and H₂S concentrations may exceed benchmark risk levels during applications of metam sodium. However, most exposure studies assessed only MITC concentrations. Risk assessment of metam sodium use based only on MITC may significantly underestimate human health risks. The combined risk of exposure to the mixture of irritants is the most relevant benchmark by which risk management strategies for metam sodium should be measured. To adequately characterize the risk resulting from a metam sodium application, exposure data for all toxic breakdown products is necessary. Further air monitoring studies to assess exposures resulting from metam-sodium application are needed, and should include assessment of MITC, MIC and H₂S.
46. Potential health risks from chronic exposures to MITC remain uncertain. MITC may have oncogenic potential, as discussed above in finding #25. The possibility of oncogenicity suggested by the MITC data is supported by the observation that tumors were produced in drinking water studies with metam-sodium. Clear genotoxicity of MIC, which is produced metabolically from MITC, is additional supporting evidence. There is an overall consistency in the data across these three compounds that suggest a potential cancer risk from metam-sodium use.
47. The potency of MITC as a dermal and pulmonary sensitizer in humans is uncertain. Sensitization by MITC following metam sodium applications might also be enhanced by co-exposures to MIC and other irritants.
48. No sensitive sub-populations have been specifically identified for metam-sodium by-products, although it has been observed that people with pre-existing respiratory conditions can be especially vulnerable to chemicals with respiratory irritant and sensitization properties.


Conclusions

49. DPR regulations (Code of California Regulations, Title 3, Section 6890(b)) specify that if pesticide air concentrations exceed levels that would result in a 10-fold lower risk than those determined to constitute a negligible risk, then the pesticide shall be identified as a Toxic Air Contaminant. Such is the case for MITC, based on the MOEs for acute and seasonal exposure at application sites.
50. The Panel has reviewed the draft version of the DPR report, "Evaluation of Methyl Isothiocyanate (MITC) as a Toxic Air Contaminant" as well as the scientific procedures and methods used to support the data, the data itself and the conclusions and assessments on which the report is based. The Panel has also reviewed and considered public comments

including those submitted by the Metam Sodium Task Force, and agency responses to comments. The Panel concludes that the report, with the revisions specified by the SRP, is based upon sound scientific knowledge, and represents a balanced assessment of our current scientific understanding.

51. The Panel recommends that the Director of DPR initiate regulatory steps to list MITC as a Toxic Air Contaminant pursuant to FAC §14023(d). In addition, because MITC in air derives overwhelmingly from applications of metam sodium, with a smaller part contributed by metam potassium and dazomet, we recommend that these three pesticides be listed as TACs. Other pesticides, not noted in this document, that break down to MITC should also be identified as TACs. Other breakdown products resulting from metam sodium use must also be considered. MIC and CS₂ are automatically listed as TACs due to their status as Hazardous Air Pollutants. Hydrogen sulfide should be identified as a TAC, based on its known toxicity and release as a breakdown product of metam sodium.

I certify that the above is a true and correct copy of the findings adopted by the Scientific Review Panel on April 26, 2002.



John R. Froines, Ph.D.
Chairman
Scientific Review Panel

8/8/02